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ORAL FORMULATION OF LIPID SOLUBLE THIAMINE AND LIPOIC ACID

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part application of earlier filed U.S. Patent Application Serial No. 10/412,559, filed April 11, 2003 which is a continuation of Serial No. 09/755,890, filed January 5, 2001 (now issued U.S. Patent 6,572,888 issued June 3, 2003) which is a continuation-in-part of earlier filed patent application Serial No. 09/288,245, filed April 8, 1999 (now issued U.S. Patent 6,197,340 issued March 6, 2001), which is a continuation-in-part of earlier filed provisional patent application Serial No. 60/102,605, filed October 1, 1998 and patent application Serial No. 09/112,623, filed July 9, 1998, which is the converted patent application of provisional patent application Serial No. 60/087,203, filed May 28, 1998 to which we claim priority under 35 U.S.C. §120 and §119(e) each of which is incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The invention relates generally to the treatment of diabetes mellitus with an oral formulation which may be a controlled release oral formulation of pharmaceutically active compounds. More particularly the invention relates to an oral formulation of a lipid soluble thiamine combined with lipoic acid.

BACKGROUND OF THE INVENTION

[0003] Vitamin B1 (Thiamine or thiamin), the first B vitamin benefits the nervous system and mental attitude. Its odor and flavor are similar to those of yeast. Thiamine can be destroyed by the cooking process, especially by boiling or moist heat, but less by dry heat, such as baking.

[0004] Like most other B vitamins, thiamine is needed in regular supply, though after its absorption from the upper and lower small intestine, some B1 is stored in the liver, heart, and kidneys. Most excess thiamine is eliminated in the urine; some seems to be excreted in the sweat as well.

[0005] Since thiamine is lost in cooking and is depleted by use of sugar, coffee, tannin from black teas, nicotine, and alcohol, it is necessary to insure that intake of thiamine is optimal. There are a number of food sources for thiamine; however, they may not be the everyday fare for many people. Good sources of vitamin B1 include the germ and bran of wheat, rice husks (outer covering), and the outer portion of other grains. With the milling of grains and use of refined flours and white or "polished" rice, many of us are no longer getting the nourishment of thiamine that is available when we eat wholesome, unprocessed foods.

[0006] Other good sources of thiamine besides wheat germ and bran, whole wheat or enriched wheat flour, and brown rice are brewer's yeast and blackstrap molasses. Oats and millet have modest amounts, as do many vegetables, such as spinach and cauliflower, most nuts, sunflower seeds, and legumes, such as peanuts, peas, and beans. Of the fruits, avocado is the highest in vitamin B1. Pork has a high amount of this B vitamin. Many dried fruits contain some thiamine, though the sulfur dioxide often added as a preservative seems to destroy this vitamin.

[0007] Thiamine helps a great many bodily functions, acting as the coenzyme thiamine pyrophosphate (TPP). It has a key metabolic role in the cellular production of energy, mainly in glucose metabolism. Thiamine is also needed to metabolize ethanol, converting it to carbon dioxide and water. B1 helps in the initial steps of fatty acid and sterol production. In this way, thiamine also helps convert carbohydrate to fat for storage of potential energy.

[0008] Thiamine is important to the health of the nerves and nervous system, possibly because of its role in the synthesis of acetylcholine (via the production of acetyl CoA), an important neurotransmitter. With a lack of vitamin B1, the nerves are more sensitive to inflammation. Thiamine is linked to individual learning capacity and to growth in children. It is also important to the muscle tone of the stomach, intestines, and heart because of the function of acetylcholine at nerve synaptic junction. It is conceivable that adequate thiamine levels may help prevent the accumulation of fatty deposits in the arteries and thereby reduce the progression of atherosclerosis.

[0009] Thiamine is used to treat any of the symptoms of its deficiency or its deficiency disease beriberi (discussed below). It is used in the treatment of fatigue, irritability, low morale, and depression and to prevent air- or seasickness. It is beneficial to the nerves, heart, and muscular system function well. By aiding hydrochloric acid production, thiamine may help digestion or reduce nausea, and it can remedy constipation by increasing intestinal muscle tone. Thiamine is used commonly to improve healing after dental (or, often, any) surgery.

[0010] Increased thiamine intake may be administered for numerous mental illnesses and problems that affect the nerves. These include alcoholism and its nerve problems, multiple sclerosis, Bell's palsy (a facial nerve paralysis), and neuritis. Treatment with thiamine, for example, has been helpful in decreasing the sensory neuropathy that accompanies diabetes and in lessening the pain of trigeminal neuralgia. Thiamine also has a mild diuretic effect and is supportive of heart function, so it is suggested in the treatment program for many cardiovascular problems.

[0011] Lipid soluble forms of thiamine include benfotiamine and prosultiamine. When these compounds are orally administered they provide greater bioavailability as compared to water soluble versions of conventional thiamine (see Greg et al., *Internation. J. Clinical Pharm. And Therapeutics*, Vol. 36, No. 4, pages 216-221 (1998)) Benfotiamine in combination with vitamine B has been used in the treatment of diabetic polyneuropathy. (See Stracke et al., *Exp.Clin. Endocrinal Diabetes*, vol. 104, pages 311-316 (1996)).

[0012] A compound known as α-lipoic acid was first isolated by Reed and coworkers as an acetate replacing factor. It is slightly soluble in water, and soluble in organic solvents. α-lipoic acid is a chiral molecule and is known by a variety of names, including thioctic acid; 1,2-diethylene-3 pentanoic acid; 1,2-diethylene-3 valeric acid; and 6,8-thioctic acid. α-lipoic acid was tentatively classified as a vitamin after its isolation, but it was later found to be synthesized by animals and humans. The complete enzyme pathway that is responsible for the *de novo* synthesis has not yet been definitively elucidated. Several studies indicate that octanoate serves as the immediate precursor for the 8-carbon fatty acid chain, and cysteine appears to be the

source of sulfur. As a lipoamide, it functions as a cofactor in the multienzyme complexes that catalyze the oxidative decarboxylation of α-keto acids such as pyruvate, α-keto glutarate, and branched chain α-keto acids.

[0013] More recently, a great deal of attention has been given to possible antioxidant functions for α-lipoic acid, and its reduced form, dihydrolipoic acid (DHLA). Lipoate, or its reduced form, DHLA, reacts with reactive oxygen species such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals, and singlet oxygen. It also protects membranes by interacting with vitamin C and glutathione, which may in turn recycle vitamin E. In addition to its antioxidant activities, DHLA may exert prooxidant actions to reduction of iron. α-lipoic acid administration has been shown to be beneficial in a number of oxidative stress models such as ischemia-reperfussion injury (IRI), diabetes (both α-lipoic acid and DHLA exhibit hydrophobic binding to proteins such as albumin, which can prevent glycation reactions), cataract formation, HIV activation, neurodegeneration, and radiation injury. Furthermore, lipoate can function as a redox regulator of proteins such as myoglobin, prolactin, thioredoxin, and NF-κB transcription factor.

[0014] Lipoate may also have other activities. For example, DHLA has been found *in vitro* to be an anti-inflammatory agent which at the same time interferes with nitric oxide release from inflammatory macrophages and protects target cells from oxygen radical attack. V. Burkhart, Dihydrolipoic Acid Protects Pancreatic Islet Cells from Inflammatory Attack, Agents Actions **38**:60 (1993). This document, and all other documents cited to herein, is incorporated by reference as if reproduced fully herein.

[0015] Lipoic acid is a coenzyme for several enzymes. Lipoic acid is a coenzyme for both α-keto acid dehydrogenase complex enzymes (i.e. pyruvate dehydrogenase complex and α-keto glutarate dehydrogenase complex), branched chain α-keto acid dehydrogenase complex, and the glycine cleavage system. In the enzyme system, the body forms a multi-enzyme complex involving lipoic acid, that breaks down molecules of pyruvate produced in earlier metabolism, to form slightly smaller, high energy molecules, called acetyl-coenzyme A. This results in molecules that can enter into a series of reactions called the citric acid cycle, or Krebs cycle, which finishes the conversion of food into energy. Essentially, lipoic acid stimulates basal glucose transport and has a positive effect on insulin stimulated glucose uptake.

SUMMARY OF THE INVENTION

[0016] An oral formulation of a lipid soluble thiamine and lipoic acid is disclosed which formulation is comprised of these pharmaceutically active components with one or more excipient materials. A wide range of different formulations of the two main active ingredients in quick release as well as biphasic and controlled release formulations will be apparent to those skilled in the art upon reading this disclosure. The formulation of lipoic acid and lipid soluble thiamine with an excipient material is designed to obtain a desired result, *e.g.* maintain sufficient blood levels of the thiamine to support nerve regeneration and maintain sufficient blood levels of lipoic acid to reduce serum glucose levels. Both effects may combine to reduce the amount of medication (such as insulin and/or metformin hydrochloride) the patient requires to control symptoms of diabetes mellitus.

[0017] Formulations of the invention comprise two or more active components. The first is a lipid soluble thiamine, e.g. benfotiamine or prosultiamine. One, two or more different lipid soluble thiamine compounds may be present together in the formulation or may be administered in separate oral formulations in the same treatment protocol of the same patient.

[0018] The second active component is lipoic acid which may be present as a racemic mixture, as the R-(+) enantiomer in amounts from 50% to 100% (of the lipoid acid component) or as the L-(-) enantiomer in amounts from 50% to 100% (of the lipoic acid component). If it is understood that if one enantiomer is present in an amount of more than 50% the other component is present in corresponding smaller percentage amounts. For example if the R-(+) enantiomer is present in amounts of 60%, 70%, 80%, 90% or 95% the L-(-) enantiomer is present in amounts of 40%, 30%, 20%, 10% or 5% respectively.

[0019] The formulation of the invention can be used not only to control blood glucose levels and treat diabetic polyneuropathy but for other complications of diabetics including diabetic neuropathy, diabetic nephropathy, and macrovascular disease. The formulation of the invention makes it possible to obtain long term high plasma and tissue levels of lipid soluble thiamine. This allows for activation of the enzyme transketolase. When transketolase is activated, glucose is shunted into the pentose-

phosphate pathway thereby reducing toxic effects of hyperglycemia. The formulation of lipoic acid and lipid-soluble thiamine provide a unique complimentary and synergestic combination of active ingredients for treating a wide variety of manifestation of diabetes arising from the toxicity of chronically elevated plasma glucose.

[0020] One aspect of the invention is a biphasic formulation which provides a quick release of a portion of the active components of the formulation followed by controlled release of the remainder which increases the period of time that a therapeutic level of the lipid soluble thiamine and lipoic acid are continuously maintained in the patient. The therapeutic level as well as the period of time over which that level must be maintained can vary between patient based on a range of factors such as the condition of the patient and the patient's reactivity to lipoic acid and the thiamine. However, an oral formulation of the invention will maintain a therapeutic level over a period of time which is greater than that obtained with a conventional quick release formulation.

[0021] The ratio of active components to excipient material and the particular excipients used result in a formulation which allows the active components to be released quickly at first and thereafter in a controlled manner for absorption into the circulatory system. By maintaining a desired serum level of active components in blood serum the oral formulation of the invention achieves physiological effects which are superior to those obtained when higher serum levels are obtained for a short term with a quick release oral dosage formulation or a single dose injectable formulation.

[0022] By providing a biphasic formulation of active components the physiological effects are provided quickly at first to raise blood levels and then continually provided over a period of time resulting in improved nerve regeneration, reduced glucose levels and A1c levels and thereby obtaining a range of associated health benefits. The controlled release formulation of the invention shows that highly desirable therapeutic effects can be obtained by maintaining a therapeutic blood serum level of the active components over a period of time which is meaningfully longer than that obtained with a quick release formulation and results are improved by maintaining such day after day over a period of 3, 7, 10, 30, 60 or more days.

[0023] A formulation of the invention will preferably obtain initial levels of lipoic acid at substantially the same rate as a quick release formulation and thereafter maintain therapeutic levels of lipoic acid over a period which is 10% or more, more preferably 50% or more and still more preferably 100% or more longer than a quick release formulation maintains therapeutic levels. To obtain a particularly preferred result the oral formulation of the invention will quickly release a sufficient amount of lipoic acid so as to quickly obtain a therapeutic level and thereafter release lipoic acid at a rate which substantially matches the rate at which the lipoic acid is being metabolized. Accordingly, a particularly preferred biphasic formulation is designed to (1) raise lipoic acid levels quickly to a therapeutic level; and (2) thereafter maintain a therapeutic level over a maximum amount of time based on the amount of lipoic acid in the formulation and to not significantly exceed the therapeutic level.

[0024] An aspect of the invention is an oral formulation of lipoic acid, and excipient compounds which provide for controlled release.

[0025] Another aspect of the invention is a biphasic oral formulation of lipoic acid which provides an immediate release of a first portion of the formulation to quickly raise blood serum levels to a therapeutic level and a controlled release of a second portion to maintain a therapeutic level over a maximum amount of time.

[0026] An advantage of the method and formulation of the invention is that by maintaining relatively low serum levels of lipoic acid over long periods of time serum glucose levels are suppressed over long periods thereby inhibiting adverse effects which result from abnormally high serum glucose levels.

[0027] Another advantage of the invention is that by administering the formulation over long periods the patient is provided with a reduced risk of developing insulin resistance and/or diabetes mellitus.

[0028] Another aspect of the invention is that the formulation provides a method of treating type 2 diabetes, i.e. non-insulin-dependent diabetes mellitus (NIDDM).

[0029] Yet another aspect of the invention is that the lipoic acid may be present as a racemic mixture or with the R-(+) enantiomer present in amounts greater than 50% and constituting up to 100% of lipoic acid in the formulation.

[0030] An advantage of the invention is that a convenient oral delivery dosage form is used to obtain the results which are superior to a single dose injectable.

[0031] Another advantage of the invention is that glucose levels can be reduced and be maintained at levels substantially below levels without treatment via the present invention.

[0032] A feature of the invention is that the oral formulation may be a tablet, capsule, caplet, etc. containing any desired amount of lipoic acid.

[0033] Another aspect of the invention is that it may be formulated with one or more additional antidiabetic agents e.g. sulfonylureas; biguanides and thiazolidinediones which agents may be formulated for quick release, controlled release or in a biphasic formulation.

[0034] Another aspect of the invention is a method of treatment whereby sustained low levels of lipoic acid blood serum over long periods continually stimulate basal glucose transport.

[0035] These and other objects, aspects, advantages, and features of the invention will become apparent to those persons skilled in the art upon reading the details of the invention as more fully described below.

BRIEF DESCRIPTION OF THE DRAWING

[0036] The invention is best understood from the following detailed description when read in conjunction with the accompanying drawings. It is emphasized that, according to common practice, the various features of the drawings are not to-scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:

[0037] Figure 1 is a conceptualized graph comparing a quick release oral dosage formulation to a biphasic lipoic acid oral dosage formulation wherein the amount released over time is graphed.

DETAILED DESCRIPTION OF THE INVENTION

[0038] Before the present, formulations, methods and components used therein are disclosed and described, it is to be understood that this invention is not limited to particular compounds, excipients or formulations as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing

particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0039] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0040] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided are subject to change if it is found that the actual date of publication is different from that provided here.

DEFINITIONS

[0041] The term "lipoic acid" is intended to mean α-lipoic acid which is a chiral molecule also known as thioctic acid; 1,2-diethylene-3 pentanoic acid; 1,2-diethylene-3 valeric acid; and 6,8-thioctic acid. Unless specified the term covers the racemic mixture as well as any other (non-50/50) mixture of the enantiomers including substantially pure forms of either the R-(+) or the S-(-) enantiomer. Further, unless specified otherwise the term covers pharmaceutically acceptable salts (e.g. Na and K salts) and amides, esters and metabolites of the acid. The molecule formula is $C_8H_{14}O_2S_2$ the molecular weight is 206.32 and it has a pKa of 4.7. In referring to pharmaceutically acceptable salts the term is intended to encompass a conventional term of pharmaceutically acceptable acid addition salts which refer to salts which retain the biological effectiveness and properties of the free-base form of the acid and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malconic acid, succinic acid, maleic acid, fumaric,

tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. The same is true with respect to amides, esters and metabolites that is those forms which can be formed and maintain biological effectiveness and not have significant undesirable biological properties.

[0042] The term "excipient material" is intended to mean any compound forming a part of the formulation which is intended to act merely as a carrier i.e. not intended to have biological activity itself.

[0043] The term "chemical degradation" is intended to mean that the lipoic acid active ingredient is subjected to a chemical reaction which disrupts its biological activity.

[0044] The terms "treating", and "treatment" and the like are used herein to generally mean obtaining a desired pharmacological and physiological effect. The effect may be prophylactic in terms of preventing or partially preventing a disease, symptom or condition thereof and/or may be therapeutic in terms of a partial or complete cure of a disease, condition, symptom or adverse effect attributed to the disease. The term "treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e. arresting it's development; or (c) relieving the disease, i.e. causing regression of the disease and/or it's symptoms or conditions. The invention is directed towards treating patient's suffering from a disease related to diabetes mellitus including adverse effects due to abnormally high levels of glucose as well as diabetic polyneuropathy and the effects of free radicals and/or oxidizing agents over long periods of time. The present invention is involved in preventing, inhibiting, or relieving adverse effects attributed to high levels of serum glucose over long periods of time and/or are such caused by free radicals or oxidizing agents present in a biological system over long periods of time.

[0045] The terms "synergistic", "synergistic effect" and the like are used interchangeably herein to describe improved treatment effects obtained by combining controlled release lipoic acid formulations of the invention with a lipid soluble thiamine and optional with one or more other orally effective diabetic compounds. Although a synergistic effect in some fields means an effect which is more than

additive (e.g., one plus one equals three) in the field of treating diabetes and related diseases an additive (one plus one equals two) or less than additive (one plus one equals 1.6) effect may be synergistic. For example, if a patient has an abnormally high glucose level, e.g. 400 mg/dl, that patient's glucose level might be reduced to 300 mg/dl by the conventional orally effective antidiabetic compound. Further, at a different time the same patient with a glucose level of 400 mg/dl might be administered a different orally effective antidiabetic compound which compound reduced the patient's glucose levels from 400 to 300 mg/dl. However, if both orally effective antidiabetic compounds are administered to the patient one would not ordinarily expect an additive effect thereby obtaining a reduction to 200 mg/dl and may obtain no more of a reduction in glucose level than when either drug is administered by itself. If additive effects could always be obtained then diabetes could be readily treated in all instances by coadministering several different types of orally effective antidiabetic compounds until the disease is cured – but this approach is not an effective treatment. However, in connection with the present invention coadministration of formulations of controlled release lipoic acid with a lipid soluble thiamine will obtain results which are synergistic, i.e. greater than the effects obtained by the administration of either composition by itself. The two active compounds may be further administered with one or more additional orally effective antidiabetic compounds such as metformin hydrochloride to obtain a further synergistic result.

[0046] The term "quick release formulation" refers to a conventional oral dosage formulation. Such a formulation may be a tablet, capsule, pill, liquid suspension or the like designed to provide for substantially immediate release of the active ingredient and includes enteric coated oral formulations which provide some initial protection to the active ingredient and thereafter allow substantially immediate release of substantially all the active ingredient. A quick release formulation is not formulated in a manner so as to obtain a gradual, slow, or controlled release of the active ingredient.

[0047] The terms "biphasic formulation," "biphasic dosage form" and the like are used interchangeably here to describe any oral formulation with two different release rates. As an example, the biphasic formulation provides for an immediate release of a first portion of both the lipoic acid and the lipid soluble thiamine followed by a slower,

controlled and metered release of a second portion of the remainder of the lipoic acid and the lipid soluble thiamine. Thus, a biphasic formulation of the invention preferably quickly raises blood levels to a therapeutic level of both active components and thereafter provides for a slower release which maintains the therapeutic level over a substantially longer time as compared to a quick release (10%, 50%, 100% or 200% longer) preferably without significantly exceeding the therapeutic level.

[0048] Thimiane or vitamin B_1 is C_{12}, H_{17}, ON_4, S HCI or thiamine hydrochloride. The compound is soluble in water and insoluble in ether and lipids. The RDA for vitamin B1 is about 1.2 mg. per day, or 1.4 mg. during pregnancy or lactation. Infants need more per body weight though less in total, about 0.5 mg. per day. Thiamine needs are based on many factors; given good health, we need about 0.5 mg. per 1,000 calories consumed, since B1 is required for energy metabolism. So our needs are based on body weight, calorie consumption, and the amount of vitamin B1 synthesized by intestinal bacteria, which can vary greatly from person to person.

[0049] Thiamine is a coenzyme for the decarboxylation of pyruvate and the oxidation of alpha keto-glutamic acid. Lipoic acid which is formed in the liver is also required for the reactions. Patients with liver disease may show signs of B1 deficiency, possibly because of deficient synthesis of lipoic acid. In vitro, thiamine deficiency produces accumulation of pyruvate and lactate, reduction of acetate, citrate and alpha-keto-glutarate and reduced acetylcholine synthesis. Any of these metabolic changes could be involved in dysfunction.

[0050] The term "lipid soluble thiamine" is used here to cover derivatives of thiamine with higher solubility in lipids as compared to thiamine., e.g. 10%, 50%, 100%, 200% or 10 times or more, more soluble in lipids as compared to thiamine. Specific lipid soluble thiamines include benfothiamine and prosultiamine. The term as used here is intended to cover pharmaceutically acceptable salts, acids, and esters thereof.

FORMULATION IN GENERAL

[0051] Referring to figure 1 which is a conceptualized graph provided to show a comparison between a theoretical quick release and theoretical biphasic oral formulation. The graph shows the amount of the active components in the patient over time. The light dashed line 1 is of a theoretical quick release oral formulation

showing that the level of active component rises and falls quickly. The bold dashed line 2 is of a theoretical controlled release formulation which initially rises more slowly as compared to the quick release formulation after reaching the therapeutical level shown by the solid line 3 it enters the controlled release phase and maintains a level at or just above the therapeutic level until no more active component is available in the dosage form. At this point the line drops to zero quickly as there is no more active component in the formulation for release and remaining active component is metabolized.

[0052] The dotted line 4 shows the release rate of a biphasic formulation. In the first phase, release rate of the active component is substantially the same as the quick release formulation. The biphasic formulation reaches the therapeutic level at substantially the same time as the quick release formulation does. Thereafter, the biphasic formulation begins a slower release as compared to the quick release formulation. For example, the rate of release of active component in the second phase is substantially equal to the rate at which the active components are metabolized. As with the controlled release formulation the object is to keep the level as close to the therapeutic level as possible for as long as possible.

[0053] In one aspect of the invention the two active components are separately formulated with excipient and thereafter combined. This is done because lipoic acid is metabolized more quickly as compared to lipid soluble thiamines. In one embodiment the lipid soluble thiamine is all in a quick release formulation and combined with lipoic acid in a biphasic formulation, i.e. both quick release and controlled release formulation. Such a formulation obtains enhanced bioavailability of a thiamine by using a lipid soluble molecule and increases the length of time that therapeutic levels of lipoic acid are maintained via the biphasic release formulation of that component.

[0054] The formulation of the invention is preferably an oral dosage formulation which may be in any suitable oral form including tablets, pills, capsules, caplets, liquid suspensions, etc. The dosage may be of any desired size in terms of the two active ingredients. However, sizes for the combined two active ingredients in a range of about 50 mg to about 1,000 mg are generally used, or for example 100 mg to 500 mg or alternatively about 200 mg to about 400 mg.

[0055] Therapeutic results can, in some cases be obtained with very small amounts of lipid soluble thiamine such as 0.5, 1.0, or 5 mg. The amount can range from 0.5 to 500 mg or be 10 to 100 mg or 30 to 70 mg or 40 to 60 mg or about 50 mg per dose. These amounts can be total amounts per day or can be modified to be amounts per day per 1,000 calories consumed by the patient.

[0056] Although the ratio of lipoic acid to lipid soluble thiamine can vary the ratio may be about 10:1, 8:1, 6:1, 4:1, 2:1 of lipoic:thiamine

[0057] The biphasic formulation is constructed to hold the active components in different combinations of excipients. Preferably the center portion of the formulation will be produced in accordance with the examples provided here. The outer portion of the formulation could be the active components alone or mixed with any excipients in the same proportional amounts generally used by those of ordinary skill in the art in producing a conventional quick release formulation.

[0058] The quick release portion may comprise from about 10% to about 50% of the active components in the formulation or preferably about 20% to about 30% and more preferably about 25% of the active components in the formulation.

[0059] The amount a patient will need to obtain an optimum therapeutical effect will vary with a number of factors known to those skilled in the art e.g. the size, age, weight, sex and condition of the patient. The patient may begin with daily doses of about 300 mg of lipoic acid and 50 mg of benfotiamine and determine if desired results are obtained, e.g. glucose levels are reduced to acceptable levels. If the desired results are not obtained in one week the daily dosage amount can be increased in increments for both of the active components. For example, lipoic acid increases can be in amounts of 100 to 300 mg/day up to any useful amount e.g. 2,000 mg/day. Longer time periods such as 3 month, 6 months, 12 months or longer may be required to observe improved results in other areas such as decreases in diabetic polyneuropathy.

[0060] A suggested dosage is to administer two tablets in the morning and administer one tablet four hours later and repeat daily over five or more days where the tablet comprise 300 mg of lipoic acid and 50 mg of benfotiamine. The larger initial dosage has been found effective in obtaining a desired effect which after being obtained can be maintained by a lower dose. Thus, a biological system may be "kick started" by a

high therapeutic level and then maintained at a lower level which is also therapeutic in terms of obtaining a desired result. In a particularly preferred formulation the benfotiamine is present as 50 mg of quick release and 75 mg of the 300 mg of lipoic acid is in a quick release formulation in the outer shell of the tablet and the inner 225 mg is in a controlled release formulation.

[0061] The manufactured compound α-lipoic generally exists as a 50/50 or racemic mixture of R-(+)-α-lipoic acid and S-(-)-α-lipoic acid. The R-(+) enantiomer is the naturally produced biological form of the compound and as such is believed to be largely responsible for obtaining the physiological effect of the lipoic acid component. Thus, the lipoic acid ingredient of the formulation of the present invention may be 100% R-(+) enantiomer. However, the active ingredient may be present in any mix of the two enantiomers e.g. 10% S-(-) and 90% R-(+); 25% S-(-) and 75% R-(+). Further, it should be noted that even though the R-(+) enantiomer is believed to be the more active the S-(-) enantiomer may possess unique properties which make inclusion of the S-(-) enantiomer important in any formulation used in treatment. Unless stated otherwise information disclosed here refers to formulations containing a racemic mixture. If the active ingredient is not a racemic mixture then some adjustment may be needed in the formulation in order to account for the greater activity of the R-(+) enantiomer as well as the slightly longer half life of the R-(+) enantiomer compared to the S-(-) enantiomer.

[0062] A typical formulation contains about 50-70% by weight active ingredient with the remainder being excipient material. The quick release portion of the formulation may comprise 100% active components or a very small amount e.g. 5-10% by weight of excipient. The controlled release portion of the formulation may comprise 55% to 65% active ingredient and more preferably about 60% active ingredient by weight. Thus, a particularly preferred oral formulation of the invention comprises about 300 mg of lipoic acid , 50 mg of benfotiamine or prosultiamine and about 200 mg of excipient material. Human patients generally eat during the day and sleep at night. Eating causes increased glucose levels. Accordingly, it is generally preferable to give a larger dose of lipoic acid at the beginning of the day. This may include two of 300 mg of lipoic acid and 50 mg of benfotiamine tablets or a single 700 mg tablet. Later

in the day (about 4 hours) the patient will take an additional 350 mg for a typical daily dose of about 900 mg of lipoic acid and 150 mg of benfothiamine for a 70 kg man.

[0063] The formulation is characterized by (a) protecting the active ingredient (to the extent required) from chemical degradation in a patient's gastrointestinal tract and (b) releasing the active ingredient in a controlled manner. By gradually releasing the active ingredient the serum levels of the active components obtained are (1) lower than those obtained with single dose injectable or a non-controlled release formulation; and (2) maintained over longer periods of time than obtained with single dose injectable or a non-controlled release formulation. A preferred biphasic formulation of the invention releases active ingredient so as to obtain a blood serum level in a human patient in a range of about 25 to 2,500 ng/ml of plasma for lipoic acid and 5 to 500 ng/ml of plasma for benfotiamine The range is preferably about 50 to 2,000 ng/ml of plasma and more preferably about 1,800 ng/ml of plasma -20% for lipoic acid and 10 to 400 ng/ml of plasma for lipid soluble thiamine. The plasma level that is therapeutic will vary somewhat from patient to patient depending on factors such as the weight, sex and age and condition of the patient and will vary further depending on the therapy or treatment being sought.

[0064] Some characteristics of lipoic acid are (1) it is non-toxic at relatively high levels, i.e. levels well in excess of therapeutic levels; and (2) lipoic acid is quickly metabolized by human patients. The present invention relies in part on the discovery that lipoic acid provides desirable therapeutic results even at very low levels provided those low levels are maintained over an extended period of time whereas therapeutic results are not obtained (even with higher levels) if the therapeutic level is not maintained over a sufficiently long period of time. Further, the present invention relies in part on the discovery that therapeutic results are further improved if the delivery of lipoic acid is administered over a period of five or more, preferably thirty or more consecutive days with long periods (four hours, eight hours, or 12 hours or more) of therapeutic levels of lipoic acid being obtained on each of the days. Another aspect of the invention is the synergistic effect obtained by comfirming the effects of lipoic acid with a thiamine. Yet another aspect of the invention is the improved bioavailability of a lipid soluble thiamine as compared to a water soluble thiamine.

[0065] One aspect of the invention is that a range of highly desirable therapeutic effects are obtained even when the lipoic acid blood serum levels are maintained in a range well below those previous used. The present invention could obtain desired therapeutic effects with higher levels of lipoic acid in blood serum. However, at least minimum levels would need to be constantly maintained over a long period of time (4 hours or more per day) for a plurality of days to obtain the desired results. When the oral dosage form is designed to obtain the lowest possible therapeutic level over the longest possible time period the results obtained are maximized and the amount of drug needed is minimized.

[0066] The lipoic acid blood plasma level obtained via the present invention is insufficient to obtain a desired therapeutic effect if that level is maintained for only a short period of time. The amount of time and the level needed can vary based on factors such as the condition of the patient and the results desired. In general, longer periods at a sustained level are preferred to short periods and large fluctuation in levels. By using the biphasic oral formulation of the invention therapeutic lipoic acid blood plasma levels can be maintained over 8 hours or more, preferably over 12 hours or more and more preferably over 16 hours or more per day. Further, those lipoic acid blood plasma levels over these periods of time are repeatedly obtained on consequetive days, preferably weeks or months and more preferably continuously over any period during which the patient would benefit from reduced serum glucose levels -- which may be the remainder of the patient's life.

[0067] To obtain the desired results a formulation of the invention needs to start with a sufficient amount of lipoic acid such that it is capable of releasing enough lipoic acid per unit of time to obtain the desired lipoic acid serum levels while compensating for lipoic acid which is metabolized. To obtain the desired results the biphasic formulation provides an initial release of lipoic acid quickly and thereafter provides a gradual release which slows over the useful life of the formulation. Desired results can be obtained with a single phase controlled release formulations where the release may be gradual from the beginning. In either case there is preferably a gradual slowing of the rate of release which is compensated for in that some of the previously released lipoic acid remains in the blood serum unmetabolized.

[0068] A preferred oral formulation is a tablet which is designed to provide an initial quick release of a portion of the lipoic acid, e.g. about 25% and thereafter dissolve gradually over a period of about 8 hours. As the tablet dissolves its reduced size will release smaller and smaller amounts of lipoic acid per unit of time. However, because the individual's system already contains a therapeutic level of lipoic acid the slower release rate is sufficient to match the rate of lipoic acid being metabolized and such will result in maintaining a relatively constant therapeutic level as shown in figure 1. At the end of the time when release of lipoic acid is no longer taking place (e.g. about 4 to 8 hours) another tablet is administered and the process is repeated. To obtain the benefits of the invention the process is continually repeated over a plurality of days, weeks, months or years. By maintaining a minimal lipoic acid blood serum level over time a patient's abnormally high serum glucose levels are reduced and the long term adverse effects of elevated serum glucose levels are avoided.

COMBINATION FORMULATIONS

[0069] Lipoic acid acts directly on muscle cells to stimulate glucose transport. The effect on serum glucose reduction obtained with lipoic acid may be sufficient for some patients. However, if an insufficient glucose lowering effect results the lipoic acid may be supplemental with one or more orally effective antidiabetic agents selected from the group consisting of sulfonylureas, biguanides and thiazolidiones. Useful sulfonylureas include tolbutamide and glipizide and related compounds such as Amaryl, Pandin and Starlix. These drugs target pancreatic beta cells and stimulate these cells to release insulin. The biguanides include compounds such as metformin, phenformin and buformin. These compounds act on the liver to decrease hepatic glucose output and on the intestine to block glucose uptake into the blood. Thiazolidinediones include compounds such troglitazone, rosaglutazone and pioglitazone. These compounds are believed to sensitize muscle and fat cells to insulin.

[0070] Although all or any orally effective antidiabetics can be formulated with or administered along with the formulation of the invention it is preferable to administer metformin (particularly metformin Hydrochloride tablets sold as Glucophage7) with controlled release formulations of the invention comprising therapeutically effective

amounts of both lipoic acid and a lipid soluble thaimine. Some particularly preferred formulations include 300 mg lipoic acid (racemic or R(+) α lipoic acid), 50 mg lipid soluble thiamine (benfotiamine or prosultiamine) and 500 mg of metformin hydrochloride or if a larger dose is needed 600 mg of lipoic acid , 100 mg of lipid soluble thiamine and 1,000 mg of metformin hydrochloride. Additional enhanced effects may be obtained by taking a formulation of the invention along with vitamin C and/or vitamin E. For example a patient might take 900 mg/day of lipoic acid 50 to 100 mg/day of benfotiamine, 1,000 to 3,000 mg/day of vitamin C and 400 to 800 mg/day of vitamin E.

[0071] Example 10 provides specific examples of patient's which underwent coadministration of controlled release lipoic acid formulations of the present invention in combination with other treatments conventionally used to lower serum glucose levels. The synergistic effects were obtained, i.e. the combination of lipoic acid controlled release formulations of the invention with other therapeutic agents obtained results which were greater than results which might be expected with the administration of either composition by itself. The lipid soluble thiamine and optional antidiabetic component may be (1) solely in the quick release portion of the formulation; (2) solely in the controlled release portion of the formulation; or (3) in both portions of the biphasic formulation with any amount in either phase of the formulation.

EXCIPIENT MATERIAL

[0072] Examples provided here show that formulations of the invention may comprise different amounts and ratios of active ingredient and excipient material. Further, different excipients can be used. Particularly preferred excipients and amounts used are recited in the Examples. However, upon reading the disclosure those skilled in the art will come to understand the general concepts of the invention and will recognize that other excipients, amounts, ratios and combinations might be used to obtain the results first shown here.

[0073] The type and amount of excipient material is added to obtain a formulation with two important characteristics. First, the resulting formulation protects the active ingredient from chemical degradation in the patient's gastrointestinal tract. Although

the formulation need not protect 100% of the lipoic acid from degradation to come within the scope of the invention it may protect 90% or more, preferably 95% or more and more preferably 99% or more of the lipoic acid from degradation. Although multiple doses of an oral formulation could be taken it is preferable to design the dosage such that a single dose is taken at each dosing event - preferably three times a day and more preferably twice a day. The better the active ingredient is protected from degradation the less active ingredient is needed in the original dosage thereby reducing manufacturing costs and increasing profits. The formulation must protect at least as much of the dose as is needed to obtain a pharmacological effect and preferably obtain the desired treatment results, e.g. maintaining desired lipoic acid and thiamine serum levels needed to obtain therapeutic results, e.g.,a reduced serum glucose level over time.

[0074] Another desired characteristic of the formulation is that it does not release all of the active ingredients at one time but rather releases the active ingredients gradually over time at a controlled rate of release which rate is preferably constant over 4 hours or more. This is particularly important for the lipoic acid component because (1) lipoic acid has a relatively short half life and (2) a desired level of lipoic acid in blood serum must be maintained over a long period to obtain the desired effect. If all of the lipoic acid is released at once it will all enter the circulatory system at once and be metabolized in the liver thereby causing the lipoic acid serum level to drop below the desired level. When this occurs the effect on reducing glucose levels is suboptimal.

[0075] These examples are more generally of the controlled release core phase of the biphasic tablets. The quick release outer phase can be manufactured using pure lipoic acid alone or with minimal excipients.

TYPICAL FORMULATIONS

[0076] A typical formulation of the invention will contain about 50% to 70% by weight of lipoic acid and 5% to 15% of lipid soluble thiamine and a particularly preferred formulation will comprise 60% by weight of lipoic acid and 10% lipid soluble thiamine. Assuming a formulation with 60% by weight of lipoic acid 10% by weight of lipid soluble thiamine with the remaining 30% being excipient material

there are a number of possible components which could be used to make up that 30%. A generalized and specific description of such is provided below:

(1)	lipoic acid		60%
	lipid soluble thiamine		10%
	organic polymer		30%
		TOTAL	100%
(2)	lipoic acid		60%
	lipid soluble thiamine		10%
	organic polymer		24.5%
	Inorganics		5.5%
		TOTAL	100%
(3)	lipoic acid		60%
	lipid soluble thiamine		10%
	organic polymer		20%-30%
	Inorganics		10% or less
		TOTAL	100%
(4)	lipoic acid		60%
	lipid soluble thiamine		10%
	microcrystalline cellulose		9%
	cellulose acetate phthalate aqueous dispersion		10%
	Polyvinylpyraolidone		3%
	ethyl acetate		2.5%
	hydrous magnesium silicate (talc)		1%
	carboxy methyl ether		4%
	magnesium stearate		0.5%
		TOTAL	100%
(5)	lipoic acid		60%
	lipid soluble thiamine		10%
	microcrystalline cellulose		10-20%
	cellulose acetate phthalate aqueous dispersion		5-15%
	Polyvinylpyraolidone		1-5%

ethyl acetate	1-5%
hydrous magnesium silicate (talc)	0.5-3%
carboxy methyl ether	1-5%
magnesium stearate	0.5-1.5%
TOTAL	100%

(6)

R-(+)-α- lipoic acid	60%
benfotiamine	10%
microcrystalline cellulose, NF (Avicel PH 101)	9%
Aquacoat CPD-30 (30% solids w/w)	10%
Plasdone K29/32, USP	3%
Carbopol 974P, NF	2.5%
Talc, USP	1.0%
croscarmellose sodium, NF (Ac, di-Sol)	4.0%
Magnesium Stearate, NF	0.5%
TOTAL	100%

(7)

R-(+)- α - lipoic acid	60%
prosultiamine	10%
microcrystalline cellulose, NF (Avicel PH 101)	10-20%
Aquacoat CPD-30 (30% solids w/w)	5-15%
Plasdone K29/32, USP	1-5%
Carbopol 974P, NF	1-5%
Talc, USP	0.5-3%
croscarmellose sodium, NF (Ac, di-Sol)	1-5%
Magnesium Stearate, NF	0.5-1.5%
TOTAL	100%

ACTUAL FORMULATIONS (Zero order kinetics)

Ingredients	Percent	Mg per Tablet	Kg per Batch
Alpha lipoic acid	47.200%	300.000	3.3040
Beta hydroxypropyl cyclodextrin	10.000%	63.559	0.7000
Dicalcium phosphate	17.000%	108.051	1.1900
Glyceryl monostearate	6.000%	38.136	0.4200
Carbpol 974P	1.528%	9.712	0.1070
Methocel K4M	2.800%	17.797	0.1960
Eudragit L 30 D-55	2.500%	15.890	0.1750
Eudragot RS PO	2.500%	15.890	0.1750
Talc	0.500%	3.178	0.0350
ProSolv SMCC 50	7.500%	47.669	0.5250
Stearic acid	1.669%	10.608	0.1168
Canosil M-5 (silicon dioxide)	0.0003%	0.019	0.0002
Mag stearate	0.800%	5.085	0.0560
TOTAL	**100.000%**	**635.593**	**7.0000**
Water for cyclodextrin			583.3333 mL
Volume of Eudragit L 30 D-55			583.3333 mL

Procedures:

1. Mix cyclodextrin in 500 mL water.
2. Place lipoic acid in Bohle and slowly spray on cyclodextrin solution.
3. Add dicalcium phosphate, glyceryl monstearate, Carbopol and Methocel to bowl.
4. Blend for 3 minutes.
5. Mix both Eudragits and talc into solution. Slowly add Eudragit solution into bowl and blend for 5 minutes.
6. Place in FBD and dry on low heat (no more than 20° C inlet) until LOD moisture is 0.75-1.5%.
7. Size using 16 mesh screen swego and mill overs in Fitzmill using 065 screen.
8. Add ProSolv & lube blend. Blend for 3 minutes.
9. Press out to desired size and hardness of 12-18 kg.

Ingredients	Percent	Mg per Tablet	Kg per Batch
Alpha lipoic acid	47.200%	300.000	3.3040
Beta hydroxypropyl cyclodextrin	10.000%	63.559	0.7000
Dicalcium phosphate	16.650%	105.826	1.1655
Glyceryl monostearate	6.000%	38.136	0.4200
Carbpol 974P	1.528%	9.712	0.1070
Methocel K4M	2.800%	17.797	0.1960
Eudragit L 30 D-55	2.500%	15.890	0.1750
Eudragot RS PO	2.850%	18.114	0.1995
Talc	0.500%	3.178	0.0350
ProSolv SMCC 50	7.500%	47.669	0.5250
Stearic acid	1.669%	10.608	0.1168
Canosil M-5 (silicon dioxide)	0.0003%	0.019	0.0002
Mag stearate	0.800%	5.085	0.0560
TOTAL	**100.000%**	**635.593**	**7.0000**

Water for cyclodextrin	583.3333 mL
Volume of Eudragit L 30 D-55	583.3333 mL
Water for Eudragir solution	150.0001 mL

Procedures:

1. Mix cyclodextrin in 500 mL water.
2. Place lipoic acid in Bohle and slowly spray on cyclodextrin solution.
3. Add dicalcium phosphate, glyceryl monstearate, Carbopol and Methocel to bowl.
4. Blend for 3 minutes.
5. Mix both Eudragits and talc into solution. Slowly add Eudragit solution into bowl and blend for 5 minutes.
6. Place in FBD and dry on low heat (no more than 20° C inlet) until LOD. moisture is 0.75-1.5%.
7. Size using 16 mesh screen swego and mill overs in Fitzmill using 065 screen.
8. Add ProSolv & lube blend. Blend for 3 minutes.

Press out to desired size and hardness of 12-18 kg

[0077] Those skilled in the art will recognize that there are endless possibilities in terms of formulations and that a margin of error e.g. $\pm$ 20% or more preferably $\pm$ 10% should be accounted for with each component. Even if the formulations are limited to the relatively few compounds shown above the formulation could be changed in limitless ways by adjusting the ratios of the components to each other. An important

feature of any formulation of the invention is that both the lipoic acid and lipid soluble thiamine be present in a therapeutically effective amount. It is also important that the lipoic acid be released in a controlled manner which makes it possible to maintain therapeutic levels of lipoic acid over a substantially longer period of time as compared to a quick release formulation. A particularly preferred formulation will quickly obtain a therapeutic level of both active components and thereafter decrease the rate of release to closely match the rate at which the active components are being metabolized thereby maintaining a therapeutic level in the patient over a maximum period of time based on the amount of active components in the oral dosage formulation. Some general types of controlled release technology which might be used with the present invention are described below followed by specific preferred formulations. Although these technologies may be applied to both the lipoic acid and the lipid soluble thiamine, it is more important to use such for the lipoic acid component.

CONTROLLED RELEASE TECHNOLOGY

[0078] Controlled release within the scope of this invention can be taken to mean any one of a number of extended release dosage forms. The following terms may be considered to be substantially equivalent to controlled release, for the purposes of the present invention: continuous release, controlled release, delayed release, depot, gradual release, long-term release, programmed release, prolonged release, proportionate release, protracted release, repository, retard, slow release, spaced release, sustained release, time coat, timed release, delayed action, extended action, layered-time action, long acting, prolonged action, repeated action, slowing acting, sustained action, sustained-action medications, and extended release. Further discussions of these terms may be found in Lesczek Krowczynski, Extended-Release Dosage Forms, 1987 (CRC Press, Inc.).

[0079] There are corporations with specific expertise in drug delivery technologies including controlled release oral formulations such as Alza corporation and Elan. A search of patents, published patent applications and related publications will provide those skilled in the art reading this disclosure with significant possible controlled release oral formulations. Examples include the formulations disclosed in any of the U.S. patents 5,637,320 issued June 10, 1997; 5,505,962 issued April 9, 1996;

5,641,745 issued June 24, 1997; and 5,641,515 issued June 24, 1997. Although specific formulations are disclosed here and in these patents the invention is more general than any specific formulation. This includes the discovery that by placing lipoic acid in a controlled release formulation which maintains therapeutic levels over substantially longer periods of time as compared to quick release formulations, improved unexpected results are obtained.

[0080] The various controlled release technologies cover a very broad spectrum of drug dosage forms. Controlled release technologies include, but are not limited to physical systems and chemical systems.

[0081] Physical systems include, but are not limited to, reservoir systems with rate-controlling membranes, such as microencapsulation, macroencapsulation, and membrane systems; reservoir systems without rate-controlling membranes, such as hollow fibers, ultra microporous cellulose triacetate, and porous polymeric substrates and foams; monolithic systems, including those systems physically dissolved in non-porous, polymeric, or elastomeric matrices (e.g., nonerodible, erodible, environmental agent ingression, and degradable), and materials physically dispersed in non-porous, polymeric, or elastomeric matrices (e.g., nonerodible, erodible, environmental agent ingression, and degradable); laminated structures, including reservoir layers chemically similar or dissimilar to outer control layers; and other physical methods, such as osmotic pumps, or adsorption onto ion-exchange resins.

[0082] Chemical systems include, but are not limited to, chemical erosion of polymer matrices (e.g., heterogeneous, or homogeneous erosion), or biological erosion of a polymer matrix (e.g., heterogeneous, or homogeneous). Additional discussion of categories of systems for controlled release may be found in Agis F. Kydonieus, Controlled Release Technologies: Methods, Theory and Applications, 1980 (CRC Press, Inc.).

[0083] Controlled release drug delivery systems may also be categorized under their basic technology areas, including, but not limited to, rate-preprogrammed drug delivery systems, activation-modulated drug delivery systems, feedback-regulated drug delivery systems, and site-targeting drug delivery systems.

[0084] In rate-preprogrammed drug delivery systems, release of drug molecules from the delivery systems "preprogrammed" at specific rate profiles. This may be

accomplished by system design, which controls the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system. Fick's laws of diffusion are often followed.

[0085] In activation-modulated drug delivery systems, release of drug molecules from the delivery systems is activated by some physical, chemical or biochemical processes and/or facilitated by the energy supplied externally. The rate of drug release is then controlled by regulating the process applied, or energy input.

[0086] In feedback-regulated drug delivery systems, release of drug molecules from the delivery systems may be activated by a triggering event, such as a biochemical substance, in the body. The rate of drug release is then controlled by the concentration of triggering agent detected by a sensor in the feedback regulated mechanism.

[0087] In a site-targeting controlled-release drug delivery system, the drug delivery system targets the active molecule to a specific site or target tissue or cell. This may be accomplished, for example, by a conjugate including a site specific targeting moiety that leads the drug delivery system to the vicinity of a target tissue (or cell), a solubilizer that enables the drug delivery system to be transported to and preferentially taken up by a target tissue, and a drug moiety that is covalently bonded to the polymer backbone through a spacer and contains a cleavable group that can be cleaved only by a specific enzyme at the target tissue.

[0088] While a preferable mode of controlled release drug delivery will be oral, other modes of delivery of controlled release compositions according to this invention may be used. These include mucosal delivery, nasal delivery, ocular delivery, transdermal delivery, parenteral controlled release delivery, vaginal delivery, and intrauterine delivery.

[0089] There are a number of controlled release drug formulations that are developed preferably for oral administration. These include, but are not limited to, osmotic pressure-controlled gastrointestinal delivery systems; hydrodynamic pressure-controlled gastrointestinal delivery systems; membrane permeation-controlled gastrointestinal delivery systems, which include microporous membrane permeation-controlled gastrointestinal delivery devices; gastric fluid-resistant intestine targeted controlled-release gastrointestinal delivery devices; gel diffusion-controlled

gastrointestinal delivery systems; and ion-exchange-controlled gastrointestinal delivery systems, which include cationic and anionic drugs. Additional information regarding controlled release drug delivery systems may be found in Yie W. Chien, Novel Drug Delivery Systems, 1992 (Marcel Dekker, Inc.). some of these formulations will now be discussed in more detail.

[0090] Enteric coatings are applied to tablets to prevent the release of drugs in the stomach either to reduce the risk of unpleasant side effects or to maintain the stability of the drug which might otherwise be subject to degradation of expose to the gastric environment. Most polymers that are used for this purpose are polyacids that function by virtue or the fact that their solubility in aqueous medium is pH-dependent, and they require conditions with a pH higher then normally encountered in the stomach.

[0091] One preferable type of oral controlled release structure is enteric coating of a solid or liquid dosage form. Enteric coatings promote the lipoates' remaining physically incorporated in the dosage form for a specified period when exposed to gastric juice. Yet the enteric coatings are designed to disintegrate in intestinal fluid for ready absorption. Delay of the lipoates' absorption is dependent on the rate of transfer through the gastrointestinal tract, and so the rate of gastric emptying is an important factor. Some investigators have reported that a multiple-unit type dosage form, such as granules, may be superior to a single-unit type. Therefore, in a preferable embodiment, the lipoates may be contained in an enterically coated multiple-unit dosage form. In a more preferable embodiment, the lipoate dosage form is prepared by spray-coating granules of an lipoate-enteric coating agent solid dispersion on an inert core material. These granules can result in prolonged absorption of the drug with good bioavailability.

[0092] Typical enteric coating agents include, but are not limited to, hydroxypropylmethylcellulose phthalate, methacryclic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate. Akihiko Hasegawa, Application of solid dispersions of Nifedipine with enteric coating agent to prepare a sustained-release dosage form, Chem. Pharm. Bull. **33**: 1615-1619 (1985). Various enteric coating materials may be selected on the basis of testing to achieve an enteric coated dosage form designed *ab initio* to have a preferable combination of dissolution time, coating thicknesses and diametral crushing strength. S.C. Porter

et al., The Properties of Enteric Tablet Coatings Made From Polyvinyl Acetate-phthalate and Cellulose acetate Phthalate, J. Pharm. Pharmacol. **22**:42p (1970).

[0093] On occasion, the performance of an enteric coating may hinge on its permeability. S.C. Porter et al., The Permeability of Enteric Coatings and the Dissolution Rates of Coated Tablets, J. Pharm. Pharmacol. **34**: 5-8 (1981). With such oral drug delivery systems, the drug release process may be initiated by diffusion of aqueous fluids across the enteric coating. Investigations have suggested osmotic driven/rupturing affects as important release mechanisms from enteric coated dosage forms. Roland Bodmeier et al., Mechanical Properties of Dry and Wet Cellulosic and Acrylic Films Prepared from Aqueous Colloidal Polymer Dispersions used in the Coating of Solid Dosage Forms, Pharmaceutical Research, **11**: 882-888 (1994).

[0094] Another type of useful oral controlled release structure is a solid dispersion. A solid dispersion may be defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting (fusion), solvent, or melting-solvent method. Akihiko Hasegawa, Super Saturation Mechanism of Drugs from Solid Dispersions with Enteric Coating Agents, Chem. Pharm. Bull. **36**: 4941-4950 (1998). The solid dispersions may be also called solid-state dispersions. The term "coprecipitates" may also be used to refer to those preparations obtained by the solvent methods.

[0095] Solid dispersions may be used to improve the solubilities and/or dissolution rates of poorly water-soluble lipoates. Hiroshi Yuasa, et al., Application of the Solid Dispersion Method to the Controlled Release Medicine. III. Control of the Release Rate of Slightly Water-Soluble Medicine From Solid Dispersion Granules, Chem. Pharm. Bull. **41**:397-399 (1993). The solid dispersion method was originally used to enhance the dissolution rate of slightly water-soluble medicines by dispersing the medicines into water-soluble carriers such as polyethylene glycol or polyvinylpyraolidone, Hiroshi Yuasa, et al., Application of the Solid Dispersion Method to the Controlled Release of Medicine. IV. Precise Control of the Release Rate of a Water-Soluble Medicine by Using the Solid Dispersion Method Applying the Difference in the Molecular Weight of a Polymer, Chem. Pharm. Bull. **41**:933-936 (1993).

[0096] The selection of the carrier may have an influence on the dissolution characteristics of the dispersed drug because the dissolution rate of a component from a surface may be affected by other components in a multiple component mixture. For example, a water-soluble carrier may result in a fast release of the drug from the matrix, or a poorly soluble or insoluble carrier may lead to a slower release of the drug from the matrix. The solubility of the lipoates may also be increased owing to some interaction with the carriers.

[0097] Examples of carriers useful in solid dispersions according to the invention include, but are not limited to, water-soluble polymers such as polyethylene glycol, polyvinylpyraolidone, or hydroxypropylmethyl - cellulose. Akihiko Hasegawa, Application of Solid Dispersions of Nifedipine with Enteric Coating Agent to Prepare a Sustained-release Dosage Form, Chem. Pharm. Bull. **33**: 1615-1619 (1985).

[0098] Alternate carriers include phosphatidylcholine. Makiko Fujii, et al., The Properties of Solid Dispersions of Indomethacin, Ketoprofen and Flurbiprofen in Phosphatidylcholine, Chem. Pharm. Bull. **36**:2186-2192 (1988). Phosphatidylcholine is an amphoteric but water-insoluble lipid, which may improve the solubility of otherwise insoluble lipoates in an amorphous state in phosphatidylcholine solid dispersions. See Makiko Fujii, et al., Dissolution of Bioavailibility of Phenytoin in Solid Dispersion with Phosphatidylcholine, Chem. Pharm. Bull **36**:4908-4913 (1988).

[0099] Other carriers include polyoxyethylene hydrogenated castor oil. Katsuhiko Yano, et al., In-Vitro Stability and In-Vivo Absorption Studies of Colloidal Particles Formed From a Solid Dispersion System, Chem. Pharm. Bull **44**:2309-2313 (1996). Poorly water-soluble lipoates may be included in a solid dispersion system with an enteric polymer such as hydroxypropylmethylcellulose phthalate and carboxymethylethylcellulose, and a non-enteric polymer, hydroxypropylmethylcellulose. See Toshiya Kai, et al., Oral Absorption Improvement of Poorly Soluble Drug Using Soluble Dispersion Technique, Chem. Pharm. Bull. **44**:568-571 (1996). Another solid dispersion dosage form include incorporation of the drug of interest with ethyl cellulose and stearic acid in different ratios. Kousuke Nakano, et al., Oral Sustained-Release Cisplatin Preparations for Rats and Mice, J. Pharm. Pharmacol. **49**:485-490 (1997).

[00100] There are various methods commonly known for preparing solid dispersions. These include, but are not limited to the melting method, the solvent method and the melting-solvent method.

[00101] In the melting method, the physical mixture of a drug in a water-soluble carrier is heated directly until it melts. The melted mixture is then cooled and solidified rapidly while rigorously stirred. The final solid mass is crushed, pulverized and sieved. Using this method a super saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule may be arrested in solvent matrix by the instantaneous solidification process. A disadvantage is that many substances, either drugs or carriers, may decompose or evaporate during the fusion process at high temperatures. However, this evaporation problem may be avoided if the physical mixture is heated in a sealed container. Melting under a vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of the drug or carrier.

[00102] The solvent method has been used in the preparation of solid solutions or mixed crystals of organic or inorganic compounds. Solvent method dispersions may prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. The main advantage of the solvent method is that thermal decomposition of drugs or carriers may be prevented because of the low temperature required for the evaporation of organic solvents. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of its supposedly negligible amount of the solvent on the chemical stability of the drug.

[00103] Another method of producing solid dispersions is the melting-solvent method. It is possible to prepare solid dispersions by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into a melt of polyethylene glycol, obtainable below 70 degrees, without removing the liquid solvent. The selected solvent or dissolved lipoate may be selected such that the solution is not miscible with the melt of polyethylene glycol. The polymorphic form of the lipoate may then be precipitated in the melt. Such a unique method possesses the advantages of both the melting and solvent methods. Win Loung Chiou, et al., Pharmaceutical Applications of Solid Dispersion Systems, J. Pharm. Sci. **60**:1281-1301 (1971).

[00104] Another controlled release dosage form is a complex between an ion exchange resin and the lipoates. Ion exchange resin-drug complexes have been used to formulate sustained-release products of acidic and basic drugs. In one preferable embodiment, a polymeric film coating is provided to the ion exchange resin-drug complex particles, making drug release from these particles diffusion controlled. See Y. Raghunathan et al., Sustained-released drug delivery system I: Coded ion-exchange resin systems for phenylpropanolamine and other drugs, J. Pharm. Sciences **70**: 379-384 (1981).

[00105] Injectable micro spheres are another controlled release dosage form. Injectable micro spheres may be prepared by non-aqueous phase separation techniques, and spray-drying techniques. Micro spheres may be prepared using polylactic acid or copoly(lactic/glycolic acid). Shigeyuki Takada, Utilization of an Amorphous Form of a Water-Soluble GPIIb/IIIa Antagonist for Controlled Release From Biodegradable Micro spheres, Pharm. Res. **14**:1146-1150 (1997), and ethyl cellulose, Yoshiyuki Koida, Studies on Dissolution Mechanism of Drugs from Ethyl Cellulose Microcapsules, Chem. Pharm. Bull. **35**:1538-1545 (1987).

[00106] Other controlled release technologies that may be used in the practice of this invention are quite varied. They include SODAS, INDAS, IPDAS, MODAS, EFVAS, PRODAS, and DUREDAS. SODAS are multi particulate dosage forms utilizing controlled release beads. INDAS are a family of drug delivery technologies designed to increase the solubility of poorly soluble drugs. IPDAS are multi particulate tablet formation utilizing a combination of high density controlled release beads and an immediate release granulate. MODAS are controlled release single unit dosage forms. Each tablet consists of an inner core surrounded by a semipermeable multiparous membrane that controls the rate of drug release. EFVAS is an effervescent drug absorption system. PRODAS is a family of multi particulate formulations utilizing combinations of immediate release and controlled release mini-tablets. DUREDAS is a bilayer tablet formulation providing dual release rates within the one dosage form. Although these dosage forms are known to one of skill, certain of these dosage forms will now be discussed in more detail.

[00107] INDAS was developed specifically to improve the solubility and absorption characteristics of poorly water soluble drugs. Solubility and, in particular, dissolution

within the fluids of the gastrointestinal tract is a key factor in determining the overall oral bioavailability of poorly water soluble drug. By enhancing solubility, one can increase the overall bioavailability of a drug with resulting reductions in dosage. INDAS takes the form of a high energy matrix tablet, production of which is comprised of two distinct steps: the adensosine analog in question is converted to an amorphous form through a combination of energy, excipients, and unique processing procedures.

[00108] Once converted to the desirable physical form, the resultant high energy complex may be stabilized by an absorption process that utilizes a novel polymer cross-linked technology to prevent recrystallization. The combination of the change in the physical state of the lipoate coupled with the solubilizing characteristics of the excipients employed enhances the solubility of the lipoate. The resulting absorbed amorphous drug complex granulate may be formulated with a gel-forming erodible tablet system to promote substantially smooth and continuous absorption.

[00109] IPDAS is a multi-particulate tablet technology that may enhance the gastrointestinal tolerability of potential irritant and ulcerogenic drugs. Intestinal protection is facilitated by the multi-particulate nature of the IPDAS formulation which promotes dispersion of an irritant lipoate throughout the gastrointestinal tract. Controlled release characteristics of the individual beads may avoid high concentration of drug being both released locally and absorbed systemically. The combination of both approaches serves to minimize the potential harm of the lipoates with resultant benefits to patients.

[00110] IPDAS is composed of numerous high density controlled release beads. Each bead may be manufactured by a two step process that involves the initial production of a micromatrix with embedded lipoates and the subsequent coating of this micromatrix with polymer solutions that form a rate limiting semipermeable membrane *in vivo*. Once an IPDAS tablet is ingested, it may disintegrate and liberate the beads in the stomach. These beads may subsequently pass into the duodenum and along the gastrointestinal tract, preferably in a controlled and gradual manner, independent of the feeding state. Lipoate release occurs by diffusion process through the micromatrix and subsequently through the pores in the rate controlling semipermeable membrane. The release rate from the IPDAS tablet may be customized to deliver a drug-specific

absorption profile associated with optimized clinical benefit. Should a fast onset of activity be necessary, immediate release granulate may be included in the tablet. The tablet may be broken prior to administration, without substantially compromising drug release, if a reduced dose is required for individual titration.

[00111] MODAS is a drug delivery system that may be used to control the absorption of water soluble lipoates. Physically MODAS is a non-disintegrating table formulation that manipulates drug release by a process of rate limiting diffusion by a semipermeable membrane formed *in vivo*. The diffusion process essentially dictates the rate of presentation of drug to the gastrointestinal fluids, such that the uptake into the body is controlled. Because of the minimal use of excipients, MODAS can readily accommodate small dosage size forms. Each MODAS tablet begins as a core containing active drug plus excipients. This core is coated with a solution of insoluble polymers and soluble excipients. Once the tablet is ingested, the fluid of the gastrointestinal tract may dissolve the soluble excipients in the outer coating leaving substantially the insoluble polymer. What results is a network of tiny, narrow channels connecting fluid from the gastrointestinal tract to the inner drug core of water soluble drug. This fluid passes through these channels, into the core, dissolving the drug, and the resultant solution of drug may diffuse out in a controlled manner. This may permit both controlled dissolution and absorption. An advantage of this system is that the drug releasing pores of the tablet are distributed over substantially the entire surface of the tablet. This facilitates uniform drug absorption reduces aggressive unidirectional drug delivery. MODAS represents a very flexible dosage form in that both the inner core and the outer semipermeable membrane may be altered to suit the individual delivery requirements of a drug. In particular, the addition of excipients to the inner core may help to produce a microenvironment within the tablet that facilitates more predictable release and absorption rates. The addition of an immediate release outer coating may allow for development of combination products.

[00112] Additionally, PRODAS may be used to deliver lipoates according to the invention. PRODAS is a multi particulate drug delivery technology based on the production of controlled release mini tablets in the size range of 1.5 to 4 mm in diameter. The PRODAS technology is a hybrid of multi particulate and hydrophilic

matrix tablet approaches, and may incorporate, in one dosage form, the benefits of both these drug delivery systems.

[00113] In its most basic form, PRODAS involves the direct compression of an immediate release granulate to produce individual mini tablets that contain lipoates. These mini tablets are subsequently incorporated into hard gels and capsules that represent the final dosage form. A more beneficial use of this technology is in the production of controlled release formulations. In this case, the incorporation of various polymer combinations within the granulate may delay the release rate of drugs from each of the individual mini tablets. These mini tablets may subsequently be coated with controlled release polymer solutions to provide additional delayed release properties. The additional coating may be necessary in the case of highly water soluble drugs or drugs that are perhaps gastroirritants where release can be delayed until the formulation reaches more distal regions of the gastrointestinal tract. One value of PRODAS technology lies in the inherent flexibility to formulation whereby combinations of mini tablets, each with different release rates, are incorporated into one dosage form. As well as potentially permitting controlled absorption over a specific period, this also may permit targeted delivery of drug to specific sites of absorption throughout the gastrointestinal tract. Combination products also may be possible using mini tablets formulated with different active ingredients.

[00114] DUREDAS is a bilayer tableting technology that may be used in the practice of the invention. DUREDAS was developed to provide for two different release rates, or dual release of a drug from one dosage form. The term bilayer refers to two separate direct compression events that take place during the tableting process. In a preferable embodiment, an immediate release granulate is first compressed, being followed by the addition of a controlled release element which is then compressed onto this initial tablet. This may give rise to the characteristic bilayer seen in the final dosage form.

[00115] The controlled release properties may be provided by a combination of hydrophilic polymers. In certain cases, a rapid release of the lipoic acid may be desirable in order to facilitate a fast onset of therapeutic affect. Hence one layer of the tablet may be formulated as an immediate release granulate. By contrast, the second layer of the tablet may release the drug in a controlled manner, preferably through the

use of hydrophilic polymers. This controlled release may result from a combination of diffusion and erosion through the hydrophilic polymer matrix.

[00116] A further extension of DUREDAS technology is the production of controlled release combination dosage forms. In this instance, two different lipoic acid compounds may be incorporated into the bilayer tablet and the release of drug from each layer controlled to maximize therapeutic affect of the combination.

[00117] The α-lipoic acid of the invention can be incorporated into any one of the aforementioned controlled released dosage forms, or other conventional dosage forms. The amount of α-lipoic acid contained in each dose can be adjusted, to meet the needs of the individual patient, and the indication. One of skill in the art and reading this disclosure will readily recognize how to adjust the level of α-lipoic acid and the release rates in a controlled release formulation, in order to optimize delivery of α-lipoic acid and its bioavailability.

THERAPEUTIC INDICATIONS/LIPOIC ACID

[00118] Formulations of the present invention can be used to obtain a wide range of desirable effects. Particularly the formulations of the invention are useful in treating essentially any disease state or symptom which is treatable by long term administration of antioxidants. Further, formulations of the invention can be used in treating patients with abnormally low levels of thiamine or vitamin B1. Still further, the invention can be used in the treatment of diseases which involve carbohydrate metabolism and blood glucose disposal which includes various forms of diabetes. In addition, the inventions can be used in the treatment of diabetic polyneuropathy. Further, the invention is useful in the treatment of various adverse effects on the eyes and skin when the adverse effect are due to high levels of free radicals which can be dissipated by the presence of antioxidants or high levels of serum glucose which can be reduced by stimulating basal glucose transport. Maintaining substantially constant levels of lipoic acid provides a long term antioxidant effect which assists in immunomodulation and can result in improved liver and kidney function. Because of the long term antioxidant effect in the circulatory system the present invention has a variety of beneficial effects on the cardiovascular system. Administering the lipid soluble thiamine is useful in the alleviation of certain liver diseases as well as

neurodegenerative diseases related to diabetes. A patient infected with HIV can benefit from the enhanced effect obtained on the immune system.

[00119] Because of the very minimal toxicity of both lipoic acid and lipid soluble thiamine the formulation can be given to a wide range of patients which have different conditions from mild to serious without fear of adverse effects. Further, the controlled release formulations taught here are even safer than quick release formulations in that serum levels obtained are low compared to quick release formulations. One mild side effect experienced by some patients taking controlled release lipoic acid is mild headaches over the first few days. The headaches have not been observed with quick release formulations of lipoic acid. Patients treated with vasodilators experience the same mild headaches over the first days of treatment. The headaches are believed to be caused by the vasodilator effect allowing increased blood flow to the brain. Accordingly, controlled release formulations of the invention can be used as a vasodilator to treat patients with angina. Controlled release lipoic acid can be administered alone with the lipid soluble thiamine or with a conventional vasodilator, e.g. with a nitroglycerin transdermal patch.

[00120] The data provided here do not show specific treatments of many of the diseases or symptoms mentioned above. However, the invention is believed to be responsible for obtaining a wide range of beneficial effects particularly when the controlled release formulation is administered to patient's (e.g. on consecutive days) over long periods of time, i.e. weeks, months and years. By maintaining substantially constant therapeutic levels of lipoic acid and lipid soluble thiamine in the blood over very long periods of time a range of desirable physiological results are obtained. Stated differently by continually maintaining the constant therapeutic serum levels of the powerful antioxidant and keeping a patient's blood glucose level within a more desirable range the adverse effects obtained from free radicals and high fluctuating glucose levels are avoided.

THERAPEUTIC INDICATIONS/THIAMINE

[00121] There is no known toxicity in humans from thiamine taken orally. People have taken hundreds of milligrams daily without any harmful effect, although some may

become more stimulated than others. Thiamine injections, however, have occasionally been associated with trauma or edema.

[00122] Prolonged restriction of thiamine intake may produce a wide variety of symptoms, particularly affecting the general disposition, nervous system, gastrointestinal tract, and heart. With thiamine deficiency, as with deficiency of most any essential nutrient, symptoms range from mild to moderate depletion disorders to the serious disease state that RDA amounts usually prevent.

[00123] Beriberi is the name given to the disease caused by thiamine deficiency. There are three basic expressions of beriberi, namely childhood, wet, and dry beriberi. Childhood beriberi stunts the growth process, and in infants high-pitched scream and rapid heartbeat are associated with the disease. Wet beriberi is the classic form with edema (swelling) in the feet and legs, spreading to the body, and associated decreased function of the heart. Dry beriberi is not accompanied by swelling but seems to be manifested by weight loss, muscle wasting, and nerve degeneration. Another thiamine deficiency disease involves degeneration of the brain and affects the general orientation, attitude, and ability to walk. This has been termed the Wernicke-Korsakoff syndrome and is usually seen in people who have been addicted to alcohol for many years.

[00124] These severe problems can and do lead to death when they are not corrected with dietary change or supplemental thiamine. Before vitamin B1 was discovered, this affected many people who ate a diet consisting mainly of polished rice. Today, deficiency of this vitamin is still quite common. Although it does not usually lead to beriberi, a number of symptoms can result from a depletion of thiamine body levels. A low-B1 diet consisting of polished rice or unenriched white flour is not often the culprit in our culture. The diet that contributes to deficiency today, especially among teenagers, is high in colas, sweets, fast foods, and many other empty-calorie foods. This diet can also lead to skin problems and symptoms of neurosis, almost like a Jekyll-and-Hyde disposition.

[00125] With a deficiency of thiamine, carbohydrate digestion and the metabolism of glucose are diminished. There is a build-up of pyruvic acid in the blood, which can

lead to decreased oxygen utilization and therefore mental deficiency and even difficulty in breathing. While B1 is needed for alcohol metabolism, alcohol abuse is often associated with a poor diet and poor B1 absorption. The poor perceptions, mental states, and nerve problems that come with alcoholism may be associated with thiamine deficiency.

[00126] The first symptoms of thiamine deficiency may be fatigue, instability. These may be followed by confusion, loss of memory, depression, clumsiness, insomnia, gastrointestinal disturbances, abdominal pain, constipation, slow heart rate, and burning chest pains. As the condition progresses, there may be problems of irregular heart rhythm, prickling sensation in the legs, loss of vibratory sensation, and the muscles may become tender and atrophy. The optic nerve may become inflamed and the vision will be affected.

[00127] Generally, with low B1 the central nervous system--the brain and nerves--does not function optimally. The gastrointestinal and cardiovascular systems are also influenced greatly. Vitamin B1 levels have been shown to be low in many elderly people, especially those that experience senility, neuroses, and schizophrenia.

[00128] Since thiamine is eliminated through the skin somewhat, doses of over 50-100 mg. per day may help repel insects such as flies and mosquitos from those with "sweet blood." Other uses for increased thiamine include treatment of stress and muscle tensions, diarrhea, fever and infections, cramps, and headaches.

[00129] Thiamine needs are also increased with higher stress levels, with fever or diarrhea, and during and after surgery. Those who smoke, drink alcohol, consume caffeine or tannin from coffee or tea, or who are pregnant, lactating, or taking birth control pills all need more thiamine, possibly much more than the RDA, for optimum health.

[00130] Thiamine is needed in the diet or in supplements daily. There are some stores in the heart, liver, and kidneys; however, these do not last very long. The minimum B1 intake for those who are very healthy is at least 2 mg. per day. A good insurance level of thiamine is probably 10 mg. a day, though even higher levels may be useful in

some situations. When we do not eat optimally, have any abusive substance habits (especially alcohol abuse), or are under stress, increased levels of thiamine are recommended. An example is the B complex 50 products--that is, 50 mg. of B1 along with that amount of most of the other B vitamins--suggested as a daily regimen. The upper intake levels of thiamine should not be much more than 200-300 mg. daily. Often B1, B2 (riboflavin), and B6 (pyridoxine) are formulated together in equal amounts within a B-complex supplement. When people take higher amounts of the B vitamins, many feel a difference in energy and vitality. (Note: Riboflavin taken for any length of time is best limited to 50 mg. daily.)

EXAMPLES

[00131] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

EXAMPLE 1

[00132] In a first step, racemic α-lipoic acid is screened to a particle size range of 150 to 450 microns. The racemic α-lipoic acid is added to a granulator. Examples of granulators include a Bohle granulator and a Glatt (Ramsey, NJ) fluid bed granulator. The racemic α-lipoic acid particles become the cores for a coated particle. The cores are coated with a 30% w/w aqueous dispersion of EUDRAGIT7 (NE30 D, methacrylic acid ester) and talc. This yields coated particles with a dried coating weight equal to about 10% of the total weight of the coated particle. The inlet air temperature is kept at a temperature of 25 deg C. After drying, the coated particles are screened using a 40 mesh screen.

[00133] The resulting, free-flowing particles are then blended and directly compressed using a tableting press according to the following formula:

Racemic α-lipoic acid, coated particles 81%
METHOCEL7 K10010%
(methylcellulose)
Microcrystalline cellulose 5%
Stearic Acid 3%
Micronized silica 0.5%
Magnesium Stearate 0.5%

[00134] The resulting tablet is a sustained release formulation.

EXAMPLE 2

[00135] In a first step, R-(+)-α-lipoic acid is screened to a particle size range of 150 to 450 microns. The R-(+)-α-lipoic acid is then added to a fluid bed granulator. The R-(+)-α-lipoic acid particles become the cores for a coated particle. The cores are coated with a 30% w/w aqueous dispersion of EUDRAGIT7 (NE30 D, methacrylic acid ester) and talc. This yields coated particles with a dried coating weight equal to about 10% of the total weight of the coated particle. The inlet air temperature is kept at a temperature of 25 deg C. After drying, the coated particles are screened using a 40 mesh screen.

[00136] The resulting, free-flowing particles are then blended and directly compressed using a tableting press according to the following formula:

R-(+)-α-lipoic acid, coated particles81%
METHOCEL7 K10010%
(methylcellulose)
Microcrystalline cellulose 5%
Stearic Acid 3%
Micronized silica 0.5%
Magnesium Stearate 0.5%

[00137] The resulting tablet is a sustained release formulation.

EXAMPLE 3

[00138] In a first step, R-(+)-α-lipoic acid is screened to a particle size range of 150 to 450 microns. The R-(+)-α-lipoic acid is then added to a fluid bed granulator. The R-(+)-α-lipoic acid particles become the cores for a coated particle. EUDRAGIT7 (L/S 100, methacrylic acid ester) is dissolved in isopropyl alcohol to form a 15% w/w solution. Triethyl citrate, talc, and water are additionally added to the solution. Total solids content of the resulting mixture is 9.6% w/w. This yields coated particles with a dried coating weight equal to about 10% of the total weight of the coated particle. The inlet air temperature is kept at a temperature of 25 deg C. After drying, the coated particles are screened using a 40 mesh screen.

[00139] The resulting, free-flowing particles are then blended and directly compressed using a tableting press according to the following formula:

R-(+)-α-lipoic acid, coated particles 81%

METHOCEL7 K100 5%

(methylcellulose)

Microcrystalline cellulose 5%

Stearic Acid 3%

Micronized silica 0.5%

Magnesium Stearate 0.5%

[00140] The resulting tablet is protected from the harsh acid environment of the stomach, and is delivered to the small intestine where it is gradually released.

EXAMPLE 4

[00141] In a first step, racemic α-lipoic acid is screened to a particle size range of 150 to 450 microns. The racemic α-lipoic acid is then added to a fluid bed granulator. The racemic α-lipoic acid particles become the cores for a coated particle. EUDRAGIT7 (L/S 100, methacrylic acid ester) is dissolved in isopropyl alcohol to form a 15% w/w solution. Triethyl citrate, talc, and water are additionally added to the solution. Total solids content of the resulting mixture is 9.6% w/w. This yields coated particles with a dried coating weight equal to about 10% of the total weight of the coated particle. The inlet air temperature is kept at a temperature of 25 deg C. After drying, the coated particles are screened using a 40 mesh screen.

[00142] The resulting, free-flowing particles are then blended and directly compressed using a tableting press according to the following formula:

Racemic α-lipoic acid, coated particles 81%

METHOCEL7 K100 5%

(methylcellulose)

Microcrystalline cellulose 5%

Stearic Acid 3%

Micronized silica 0.5%

Magnesium Stearate 0.5%

[00143] The resulting tablet is protected from the harsh acid environment of the stomach, and is delivered to the small intestine where it is gradually released.

EXAMPLE 5

[00144] A preblend of 98% w/w CARBOPOL7 934 (B. F. Goodrich Chemical, lightly cross-linked acrylic acid allyl sucrose copolymer) and 2%w/w micronized silica is prepared. To this mixture, racemic α-lipoic acid, METHOCEL7 K100, stearic acid, and lactose are added according to the following formula:

Racemic α-lipoic acid preblend 70%

CARBOPOL7 934/silica preblend 10%

METHOCEL7 K10010%

stearic acid 5%

lactose 5%

[00145] The resulting mixture is tableted using a direct compression tableting press to form a bioadhesive formulation.

EXAMPLE 6

[00146] A preblend of 98% w/w R-(+)-α-lipoic acid and 2% w/w CAB-O-SIL7 micronized silica is formed. To this mixture is added guar gum (AQUALON7 G-3), polyvinylpyraolidone (PVP), calcium carbonate, stearic acid, lactose, and magnesium stearate in the following amounts:

R-(+)-α-lipoic acid/CAB-O-SIL7 blend49.5%

guar gum (AQUALON7 G-3)30%

polyvinylpyraolidone (PVP) 5%

calcium carbonate 5%

stearic acid 5%

lactose 5%

magnesium stearate 0.5%

[00147] The resulting mixture is tableted using a direct compression tableting press to form a sustained release caplet formulation.

EXAMPLE 7

Item No.	Item Description	Percent	Theoretical Quantity	Unit of Measure
1.	α-Lipoic Acid	60	4800.0	g
2.	Microcrystalline Cellulose, NF (Avicel PH 101)	18	1440.0	g
3.	Aquacoat CPD (30% w/w)	15*	4000.0*	g
4.	Povidone K29/32, USP	3	240.0	g
5.	Carbopol 974P	2.5	200.0	g
6.	Talc, USP	1	80.0	g
7.	Magnesium Stearate, NF	0.5	40.0	g
8.	Purified Water, USP		----	g
N/A	TOTAL	100	8000.0	g

* *Quantity indicates amount of dispersion to be used in granulating. Actual Solids Content-1200g - 15% is based on solids content*

[00148] Before formulating a check should be made of the room and equipment in order to verify that the cleaning procedure has been performed and approved. Weigh and charge α-Lipoic Acid (Item 1) and Avicel PH 101, (Item 2) in a Hobart Mixer and mix for two (2) minutes with the mixer speed set at 1 or 2. Granulate the Step 2

material by slowly adding Aquacoat CPD (Item 3) until granules are formed. Add additional Purified Water, USP (Item 8) if required, and mix until the granules are formed. Mixer Speed Setting remains at 1-2. Spread the granulation evenly from Step 3 on paper-lined trays and load them into the oven. Dry at 40EC∀5EC for two (2) hours. Check LOD and record moisture content. If LOD is more than 2%, continue drying until LOD is below 2%. Pass the dried material from Step 5 through a size 14 mesh screen, hand held or using a Quadro Comil. Charge the Step 6 granulation into a V-blender. Charge the Step 7 blend in blender with Povidone K29/32, USP (Item 4) and Carbopol 974P (Item 5) and mix for five (5) minutes. Charge the V-blender with Talc (Item 6) and Magnesium Stearate, NF (Item 7) and blend for three (3) minutes. Empty the blend from the V-blender into a properly labeled tared PE-lined container and record the weights in Step 11. Theoretical weight of blend: 8000.0 g. Lower Limit 95% and Upper Limit 102%. Any discrepancy from these established limits must be reported to Production and Quality Assurance. Any discrepancy must be appropriately investigated and documented. Hold the blend in the in-process Q.C. Hold area for further processing. Using the amounts shown above will result in sufficient formulations to produce above 16,000 300 mg tablets.

EXAMPLE 8

[00149] A controlled release oral dosage form of racemic α-lipoic acid was administered to a group of volunteers. Each dose consisted of a tablet containing 300 mg of racemic α-lipoic acid, compounded with calcium phosphate, starch, cellulose ethers, polycarboxylic acid, and magnesium stearate. The 300 mg tablets used with these patients were tablets prepared in a manner as described above in Example 7. Each patient was given two 300 mg tablets in the morning before eating and one 300 mg tablet within 6 to 8 hours.

[00150] The results were as follows:

			Average Glucose Levels	
Patient No.	Sex (M/F)	Age	Before	After
1	M	47	240	150
2	F	46	225	120

3	M	45	155	130
4	M	67	155	95
5	F	47	175	195
6	M	82	138	129
7	M	48	174	119
8	M	71	150	90

[00151] As can be seen from Table 1, the average glucose level before treatment with the controlled release lipoic acid was 176.5 mg/dl. After treatment with the controlled release lipoic acid, the average glucose level was 128.5 mg/dl, a average decrease of 48 mg/dl.

EXAMPLE 9

[00152] A controlled release oral dosage form of racemic α-lipoic acid was administered to a group of volunteers. Each dose consisted of a tablet containing 300 mg of racemic α-lipoic acid, compounded with calcium phosphate, starch, cellulose ethers, polycarboxylic acid, and magnesium stearate. The 300 mg tablets used with these patients were tablets prepared in a manner as described above in Example 7 and dosed in the same manner described in Example 7.

[00153] The results were as follows:

			Average Glucose Levels	
Patient No.	Sex (M/F)	Age	Before	After
1	M	62	400	140
2	F	65	300	149
3	F	51	325	185

[00154] As can be seen from Table 2, the average glucose level before treatment with the controlled release lipoic acid was 342 mg/dl. After treatment with the controlled release lipoic acid, the average glucose level was 158 mg/dl, a average decrease of 184 mg/dl.

EXAMPLE 10

[00155] Fourteen human volunteers described below were administered controlled release lipoic acid formulations of the present invention. The formulations were prepared in a manner such as that described in Example 7 above. Each patient was dosed with two 300 mg tablets in the morning before eating and one 300 mg tablet approximately six hours thereafter. In some instances some patients were dosed with additional medications as indicated. These results demonstrate the improved results with the lipoic acid controlled release formulations of the invention alone or in combination with other pharmaceutically active compositions.

New CR ALA Tablet Study
30-Nov-98

Patient #	Type	Description	Age	Average Glucose Levels Before	After	Change	Percent Change	Comments
1	Type 2	Glucophage 850mg 3x	51	220	110	-110	-50%	
2	type 2	Insulin/Glucophage	70	168	112	-56	-33%	
3	Type 2	Insulin/Oral Meds	54	175	120	-55	-31%	Cut meds in half and 9 to 7 A1C
4	Type 2	Glucophage 500mg 2x Day	65	135	114	-21	-16%	
6	type 2	Diet & Exercise	46	189	131	-58	-31%	Dr. did not have to put on drugs and drop A1C from 8.3 to 6.2
7	Type 2	GlucophageXL	67	135	90	-45	-33%	
8	Type 2	Insulin/Glucophage	46	300	200	-100	-33%	
10	Type 2	Insulin/Oral Meds	72	185	135	-50	-27%	
11	Type 2	Insulin	72	135	87	-48	-36%	
12	Type 2	Glucophage/Glucotrol	79	225	140	-85	-38%	
13	Type 2	Diet & Exercise	59	145	111	-35	-24%	
14	Type 2	"Insulin, 15 unix 2x"	51	325	191	-134	-41%	
		AVERAGE =	186	128	-57	-29%		
5	Normal	Severe polyneuropathy	#N/A	#N/A	#N/A	#N/A	#N/A	Eliminated all neuropath

EXAMPLE 11

[00156] In a first step,both a racemic a-lipoic acid and a lipid soluable thiamine are screened to a particle size range of 150 to 450 microns. The racemic a-lipoic acid and the lipid soluable thiamine are then added to a fluid bed granulator. The paricles of racemic a-lipoic acid and lipid soluable thiamine become the cores for a coated particle. EUDRAGIT7 (L/S 100, methacrylic acid ester) is dissolved in isopropyl alcohol to form a 15% w/w solution. Triethyl citrate, talc, and water are additionally added to the solution. Total solids content of the resulting mixture is 9.6% w/w. This yields coated particles with a dried coating weight equal to about 10% of the total weight of the coated particle. The inlet air temperature is kept at a temperature of 25 deg C. After drying, the coated particles are screened using a 40 mesh screen.

[00157] The resulting, free-flowing particles are then blended and directly compressed using a tableting press according to the following formula:

[00158] Racemic a-lipoic acid, coated particles 71%

[00159] Lipid soluable thiamine 10%

[00160] METHOCEL7 K100 5%

[00161] (methylcellulose)

[00162] Microcrystalline cellulose 5%

[00163] Stearic Acid 3%

[00164] Micronized silica 0.5%

[00165] Magnesium Stearate 0.5%

EXAMPLE 12

[00166] In a first step,both a racemic a-lipoic acid and benfotiamine are screened to a particle size range of 150 to 450 microns. The racemic a-lipoic acid and benfotiamine are then added to a fluid bed granulator. The paricles of racemic a-lipoic acid and lipid soluable thiamine become the cores for a coated particle. EUDRAGIT7 (L/S 100, methacrylic acid ester) is dissolved in isopropyl alcohol to form a 15% w/w solution. Triethyl citrate, talc, and water are additionally added to the solution. Total solids content of the resulting mixture is 9.6% w/w. This yields coated particles with a dried coating weight equal to about 10% of the total weight of the coated particle.

The inlet air temperature is kept at a temperature of 25 deg C. After drying, the coated particles are screened using a 40 mesh screen.

[00167] The resulting, free-flowing particles are then blended and directly compressed using a tableting press according to the following formula:

[00168] Racemic a-lipoic acid, coated particles 76%

[00169] Lipid soluable thiamine 5%

[00170] METHOCEL7 K100 5%

[00171] (methylcellulose)

[00172] Microcrystalline cellulose 5%

[00173] Stearic Acid 3%

[00174] Micronized silica 0.5%

[00175] Magnesium Stearate 0.5%

[00176] The preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims.